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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/425,075	10/21/99	CHOUDARY	P 480.97-1-(HV

HM22/1115

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EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 11/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/425,075	Choudary et al
Examiner	**Group Art Unit**
Larry R. H Ims Ph.D.	1642

☒ Responsive to communication(s) filed on *28 Aug 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *14-18* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-13 and 19-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's provisional election with traverse of Group I, claims 1-13 and 19-21, during a telephone call to Hana Verny on March 1, 2000 is acknowledged. The response to this provisional election is traversed in the response filed 8/28/2000. The traversal is on the ground(s) that "The antibody of claims 14-18, as presented, cannot be made by any other method than the one set in steps (a) through (o) ." This is not persuasive. As stated in the restriction requirement "in the instant case the antibody of Group II can be made by several different methods such as immunizing an animal with an antigen or produced in P. pastoris with different cloning steps utilizing different signal sequences and different steps to confirm the intactness of the insert, such as restriction digests, for example, in addition to the method of Group I." In addition the class and subclass for each Group is different, requiring a separate search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**

2. This application contains claims 14-18 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claims 14-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

4. Claims 1-21 are pending.

Claims 14-18 are withdrawn.

Claims 1-21 have been amended.

Claims 1-13 and 19-21 are under examination.

5. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

6. The following contains some NEW GROUNDS of rejections.

Rejections Withdrawn

7. The rejection of claims 1-13 and 19-21 under 35 U.S.C. 112, second paragraph, as applied to paragraph 10 a-I and k-m, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

8. The rejection claim 20 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of the amendment to the claim.

9. The rejection of claims 19-21 under 35 U.S.C. 102(b) as being anticipated by Eldin et al (J. of Immunological Methods 201:67-75, 2/14/97) and as evidenced by the Invitrogen 1997 catalog (published 1/97, Yeast expression pages 14-17) is withdrawn in view of the amendment to the claims.

10. The rejection of claims 4-7 under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Sambrook et al (Molecular Cloning, A Laboratory Manual Second Edition pages 1.85, 12.16-12.20, and 13.42-13.44, 1989) is withdrawn in view of the amendments to the claims.

Response to Arguments

11. The rejection of claims 1-13 under 35 U.S.C. 112, second paragraph, as applied to paragraph 10 j, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the reasons set forth in the previous Office Action.

The response has been carefully considered but is deemed not to be persuasive. The response states that claims 6 and 7 have been amended. In response to this argument, it is true that the claims have been amended, but the term "pPICZαLH" was added to claim 1. Thus, claims 1-13 remain indefinite.

12. The rejection of claims 1-3 and 8-13 under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al

(Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Sambrook et al (Molecular Cloning, A Laboratory Manual Second Edition pages 1.85, 12.16-12.20, and 13.42-13.44, 1989) is maintained.

The response has been carefully considered but is deemed not to be persuasive. The response states that "the Examiner has to combine four (4) publications available from 1988-1997...to come up with such an "obvious" method" and "Applicants suggest that the Examiner uses hindsight which makes everything obvious to him." (See page 30 and 31 of response). In addition, "While the method of Horwitz would seem to produce antibody containing both heavy and light chains, the production is extremely inefficient...compared to the current method" (see page 34-35 of response). Moreover, the response states "No person skilled in the art would have expected from either Horwitz or Cregg, one could produce a large quantity of complex multimeric proteins, i.e., antibodies in about 3-4 days." (See page 36 of response).

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so

long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Horowitz is cited for teaching production in Yeast of an antibody and with the knowledge of the Invitrogen catalog one would know to use these vectors for increased expression levels and faster and easier production of antibodies. In regards to the Sambrook reference, this reference teaches basic molecular biology techniques which would have been obvious to perform such as, screening for intact inserts, sequencing, and expression of the antibody.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. production of antibodies at 10-36 mg/l in about 12 hours to 4.5 days.) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Guens, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Although these features upon which applicant relies on are not recited in the claims such as the high level of expression, it would be obvious that the combination of references cited would

produce a high level of intact antibody in a shorter amount of time as stated in the Invitrogen catalog reference (see page 14).

Moreover, the response states that "why did no one (skilled or nonskilled) in the art come up with the current method?" (See page 36 of response). In response to this argument, the legal criteria for obviousness is set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a). The response states the criteria on page 24.

Thus, the facts remain it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an antibody in P. Pastoris comprising the claimed steps with the vectors and methods of selection, screening, detection, and binding analysis in view of Horwitz et al, Cregg et al, Sambrook et al, and the 1997 Invitrogen Catalog in order to produce antibodies in P. pastoris.

13. The rejection of claims 19-21 under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al and further in view of The 1997 Invitrogen Catalog is maintained.

The response has been carefully considered but is deemed not to be persuasive. The response states that "The question, as in the prior rejection, is why no one made such combination." (See page 38 of response) and "the yield of Horwitz production is so low that no one interested in improving a yield would have been interested to do so" (see page 39).

In response to these arguments, the same response as above can be applied to the argument of "why no one made such combination". In response to the argument that Horwitz produces a low level of antibody, the claims do not recite an amount of the antibody that needs to be produced or the amount of time or work needed to produce such an antibody. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Guens, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Although these features upon which applicant relies on are not recited in the claims, it would be obvious that the combination of references cited would produce a high level of intact antibody in a shorter amount to time as stated in the Invitrogen catalog reference (see page 14).

Thus, the fact remains that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a recombinant P. pastoris vector containing dual expression cassettes, each carrying a cDNA copy of immunoglobulin light and heavy chain and P. pastoris transformed with cDNA encoding an antibody in view of Horwitz et al and the 1997 Invitrogen Catalog.

The following are some NEW GROUNDS of rejections.

14. Claims 1-13, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-13 are indefinite for reciting "selecting an antigen against which the specific antibody is to be produced" in claim 1 because the exact meaning of the phrase is not clear. Does the antibody produced in the method have to be directed against the selected antigen or do you need to just select any antigen?

b. Claims 5-7 and 21 are indefinite in the recitation of "hybridoma DD1" in claim 5 and 21 because other laboratories/inventors may use the same laboratory designation to refer to different antibodies/hybridomas. Amendment of the claim to insert the corresponding ATCC accession number of the hybridoma which produces the antibody or to add the SEQ ID Nos of the heavy and light chain variable regions would overcome this rejection.

c. Claims 6 and 7 are indefinite for reciting "light chain cDNA from the DD1 hybridoma" and " heavy chain cDNA from the DD1 hybridoma" in claim 6 because the exact meaning of the phrases are not clear. It is not clear if the cDNA from the DNA encoding the antibody produced by hybridoma DD1 or if the cDNA is from the hybridoma cell DD1.

d. Claims 11-13 are indefinite for reciting in claim 11 "origin of the recombinant antibody" because the exact meaning of the phrase is not clear. Does the phrase mean where the antibody comes from?

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 5-7 and 21 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

a. It is unclear if a hybridoma DD1 which produces the antibody is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar

immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed hybridoma DD1 producing the antibody. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Claim Rejections - 35 USC § 103

17. Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (PNAS 85:8678-8682, 1988) as applied to claims 1-3 above, and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96), Sambrook et al (Molecular Cloning, A Laboratory Manual Second Edition pages 1.85, 12.16-12.20, and 13.42-13.44, 1989) and Vanderlaan et al (U.S. Patent 5,429,925, issued 7/4/95).

a. The claims recite the method wherein the antigen is dioxin and the antibody is isolated from a hybridoma DD1, encoded by cDNA of the light chain and heavy chain from the DD1 hybridoma and the antibody is secreted into the supernatant.

b. Horwitz et al has been described in the previous Office action. Horwitz et al does not teach a recombinant host P. pastoris transformed with a vector for expression, the AOX1-P promoter, the pPICZα vector, replacement of the yeast chromosomal AOX1 with the AOX1-

antibody DNA by homologous recombination, or selection on zeocin media or screening by colony-immunoblotting, restriction analysis, or nucleotide sequence analysis or the anti-dioxin antibody produced by DD1 Hybridoma. These deficiencies are made up for in the teachings of Cregg et al , the Invitrogen 1997 Catalog, Sambrook et al and Vanderlaan et al.

c. Cregg et al, Sambrook et al, and the Invitrogen catalog have been described in the previous Office action.

d. Vanderlaan et al teach the antidioxin antibody and the hybridoma DD1.

e. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an anti-dioxin antibody from the DD1 hybridoma in P. Pastoris comprising the claimed steps with the vectors and methods of selection, screening, detection, and binding analysis in view of Horwitz et al, Cregg et al, Sambrook et al, the 1997 Invitrogen Catalog, and Vanderlaan et al in order to produce anti-dioxin antibodies in P. pastoris.

f. One of ordinary skill in the art would have been motivated to produce the claimed method because Horwitz et al teach recombinant production of proteins, specifically, an antibody in S. cerevisiae in general with selection, screening, and purification and testing antigen binding. In addition, one of ordinary skill in the art would have been motivated to produce the claimed method in P. pastoris because Cregg et al teach production of heterologous proteins in P. pastoris overcomes the problems associated with producing commercially useful levels of proteins in S. cerevisiae (see page 33, introduction) and the P. pastoris is ideally suited for the production of

many heterologous proteins due to the fact that (1) a detailed understanding of the growth characteristics of the organism in high-density fermentors is known, (2) the ability to place foreign DNA into the genome in a precisely controlled manner, and (3) promoters are tightly regulated and efficiently transcribed to produce proteins at high levels. (See page 40). In addition, one of ordinary skill in the art would have been motivated to produce the claimed method because the Invitrogen Catalog teach a Pichia expression vector called pPICZα which is based on homologous recombination comprising; several restriction sites for cloning of recombinant proteins, a promoter (AOX1), termination sequences, selectable markers (zeocin), and α-factor secretion signal for expression in P. pastoris of antibodies (see pages 14-15 and 18). Moreover, one of ordinary skill in the art would have been motivated to construct vectors for cloning and methods of screening of transformed colonies for expression cassettes because Sambrook et al teach basic molecular biology methods for cloning and screening of transformed colonies and in view of the teachings of Sambrook one skilled in the art would also reasonably conclude that when constructing recombinant vectors one would naturally analyze the DNA sequence for integrity and intactness and perform screening methods for obtaining the desired colonies. In addition, in view of the teachings of Horwitz et al one of ordinary skill in the art would know to use the methods of Western blot for detection of the expressed protein and test the antibody for antigen binding. In addition, on e skilled in the art would be motivated to produce the claimed method because Vanderlaan et al teach the anti-dioxin antibody produced from the hybridoma DD1 and it would have been obvious to obtain the cDNA of the light and

heavy chains by the method of Horwitz et al and produce an antibody in P. pastoris because one skilled in the art would want to obtain high levels of expression and ease of purification of the antibody as taught by the Invitrogen catalog using the vectors described in the catalog and because the anti-dioxin antibody "permits detection of dioxin contaminants in industrial or environmental samples" as taught by Vandarlaan et al.

g. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Horwitz et al teach the antibodies produced in yeast were secreted and functional by binding the target antigen (see abstract). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Cregg et al teach the result of the engineered yeast is a yeast that is "easily scaled up from shake-flask to large-volume, high-density cultures with little change in the kinetics of product synthesis" (see abstract) Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because the Invitrogen Catalog teach that the expression vector and P. pastoris makes "an ideal tool for laboratory research as well as industrial applications" (see page 14).

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

18. No claim is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D., whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER